

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/022323 A1

- (51) International Patent Classification⁷: A61L 31/10, 31/16
- (21) International Application Number: PCT/US02/27521
- (22) International Filing Date: 28 August 2002 (28.08.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/948,513 7 September 2001 (07.09.2001) US
- (71) Applicant: ADVANCED CARDIOVASCULAR SYSTEMS, INC. [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (72) Inventor: PACETTI, Stephen, D.; 4578 Madoc Way, San Jose, CA 95130 (US).
- (74) Agents: KERRIGAN, Cameron et al.; Squire, Sanders & Dempsey, L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COATING FOR REDUCING THE RATE OF RELEASE OF DRUGS FROM STENTS

(57) Abstract: A stent for delivery of a therapeutic agent is disclosed. The stent includes a polymer coating for reducing the rate of release of the therapeutic agent. The polymer has a crystalline structure wherein the polymer is capable of significantly maintaining the crystalline lattice structure while the therapeutic agent is released from the stent such that the aqueous environment to which the stent is exposed subsequent to the implantation of the stent does not significantly convert the crystalline lattice structure of the polymer to an amorphous structure.

WO 03/022323 A1

COATING FOR REDUCING THE RATE OF RELEASE OF DRUGS FROM STENTS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] A medical device, such as a stent, for delivering a therapeutic substance is disclosed. The stent includes a polymeric coating for reducing the rate of release of the therapeutic substance.

Description of the Background

[0002] Blood vessel occlusions are commonly treated by mechanically enhancing blood flow in the affected vessels, such as by employing a stent. Stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically stents are capable of being compressed, so that they can be inserted through small lumens via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in the patent literature disclosing stents include U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

[0003] Stents are used not only for mechanical intervention but also as vehicles for providing biological therapy. Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. Local delivery of a therapeutic substance is a preferred method of treatment because the substance is concentrated at a specific

site and thus smaller total levels of medication can be administered in comparison to systemic dosages that often produce adverse or even toxic side effects for the patient.

[0004] One method of medicating a stent involves the use of a polymeric carrier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent. The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the therapeutic substance impregnated in the polymer.

[0005] Depending on the physiological mechanism targeted, the therapeutic substance may be required to be released at an efficacious concentration for an extended duration of time. Increasing the quantity of the therapeutic substance in the polymeric coating can lead to poor coating mechanical properties, inadequate coating adhesion, and overly rapid rate of release. Increasing the quantity of the polymeric compound by producing a thicker coating can perturb the geometrical and mechanical functionality of the stent as well as limit the procedures for which the stent can be used.

[0006] It is desirable to increase the residence time of a substance at the site of implantation, at a therapeutically useful concentration, without the addition of a greater percentage of the therapeutic substance to the polymeric coating and without the application of a significantly thicker coating.

SUMMARY OF THE INVENTION

[0007] The present invention discloses a stent for delivery of a therapeutic agent.

The stent includes a polymer coating for reducing the rate of release of the therapeutic agent. The polymer has a crystalline lattice structure, wherein the polymer is capable of significantly maintaining the crystalline lattice structure while the therapeutic agent is released from the stent such that the aqueous environment to which the stent is exposed subsequent to the implantation of the stent does not significantly convert the crystalline lattice structure of the polymer to an amorphous structure.

[0008] The coating can contain the therapeutic agent. In one embodiment, the melting point of the polymer is greater than or equal to about 135°C at ambient pressure. In another embodiment, the polymer is a hydrophobic polymer having a solubility parameter not greater than about $10.7 \text{ (cal/cm}^3)^{1/2}$.

[0009] Also disclosed is a method of forming a coating for a stent. The method includes applying a first composition including a polymeric material to at least a portion of the stent to form a polymer coating supported by the stent. The polymer has a crystalline structure, wherein the aqueous environment to which the coating is exposed subsequent to the implantation of the stent does not significantly convert the crystalline structure of the polymer to an amorphous structure for the duration of time which the agent is released from the stent.

[0010] The present invention additionally discloses a composition for coating a stent. The composition includes a fluid and a polymer dissolved in the fluid. The

polymer includes a crystalline structure during the duration of delivery of an active agent from the stent, and the aqueous environment to which the stent is exposed subsequent to the implantation procedure does not significantly change the crystalline structure to an amorphous structure.

[0011] Also disclosed is a stent for delivering a therapeutic agent to an implanted site. The stent includes a radially expandable body structure and a polymeric coating supported by the body structure for extending the residence time of the therapeutic agent at the implanted site. The polymeric coating is made from a hydrophobic polymer having a degree of crystallinity that remains at or above about 10% at least until a significant amount of the therapeutic substance has been released from the stent.

DETAILED DESCRIPTION

Embodiments of the Rate-Reducing Coating

[0012] One mechanism through which the release rate of an active agent from a medical device can be controlled is the crystallinity of the polymer with which the medical device is coated. A polymer in which the molecules are arranged in a highly ordered and regular pattern formed by folding and stacking of the polymer chains is said to be crystalline. By contrast, amorphous polymers have molecules that are arranged randomly with no regularity of orientation with respect to one another. Among the factors that affect polymer crystallinity are the stereoregularity of the polymer, the tacticity of the polymer, the presence of branching, the degree

of polymerization, and the strength of the intermolecular forces between the polymer chains.

[0013] The structural arrangement and regularity of a polymer is an important factor in the determination of polymer crystallinity. A regular arrangement along the polymer chains provides the polymer structure with a high degree of symmetry, allowing the chains to pack into crystals. Irregularity along the polymer chains, however, prevents the chains from packing closely to one another, thereby decreasing crystallinity. Polymers with regular, linear, and rigid structures tend to form ordered crystals. By contrast, polymers with large side groups, mixed tacticity or an atactic structure, a mix of side or functional groups, or composed of more than one monomer tend not to pack well into crystalline structures.

[0014] The degree of polymerization also contributes to the determination of the crystallinity of a polymer. Relatively short chains organize themselves into crystalline structures more readily than longer molecules, as longer molecules tend to become tangled and thus have difficulty arranging themselves in an ordered manner, resulting in a more amorphous structure.

[0015] Also influencing polymer crystallinity is the presence of intermolecular forces. The presence of polar and hydrogen bonding groups favors crystallinity because such groups promote dipole-dipole and hydrogen bonding intermolecular forces. Such strong interchain forces hold the polymer chains in a tightly packed configuration, thereby promoting crystallinity. By contrast, polymers with little or

no intermolecular forces will tend to have random, non-crystalline structures as a result of thermal motion.

[0016] Typically, as the crystallinity of a polymer increases, so too does the polymer's ability to reduce the rate at which an active agent is released from a medical device coated with the polymer. This is because it is more difficult for an active agent to diffuse through a tightly packed, crystalline polymer than a more loosely packed, amorphous polymer. The purpose of the coating of the present invention is to decrease the rate of release of an active agent therefrom. Accordingly, the polymer for forming the rate-reducing coating should be selected to have sufficient crystallinity such that the active agent may not readily diffuse therethrough.

[0017] The degree of crystallinity of the polymer can be measured by the amount of the polymer that is in the form of crystallites or a detectable pattern of crystals as may be observed using conventional techniques such as x-ray diffraction, measurement of specific volume, infrared spectroscopy, and thermal analysis. For use with the embodiments of the present invention, the polymer can have a crystallinity of not less than about 10%, alternatively not less than about 25%. In accordance with another embodiment the degree of crystallinity should not be less than about 50%. When exposed to an aqueous environment such as blood, the polymer can have a crystallinity of not less than about 10%, alternatively not less than 25%. In one example, the polymer can have a crystallinity of at least 50% or at least 25% in an aqueous environment, such as in contact with blood.

[0018] In addition, the crystalline polymers for use in the rate-reducing coating of the present invention should be capable of maintaining their crystallinity in the aqueous *in vivo* environment in which the coated medical device will be employed. The crystallinity of some polymers decreases when exposed to water. This is due to absorption of water by the polymer, which is also known as polymer swelling. The absorbed water can reduce or eliminate the polymer crystallinity. In extreme cases, such absorption can lead to complete dissolution of the polymer. Polymers that contain ionic, polar, or hydrogen bonding groups have the potential to absorb water. In general, if the interaction of the polymer with water is stronger than that of the polymer with itself or of water with itself, the polymer will swell with water. When a polymer swells, its chains move apart to form pores in the polymeric network, thereby increasing the diffusion rate of an active agent through the polymeric network. Accordingly, the polymers for use in the rate-reducing coating of the present invention should be selected to maintain their crystallinity, and thus their rate-reducing capabilities, in an aqueous environment.

[0019] Many crystalline polymers that are hydrophobic can maintain their crystallinity in an aqueous environment because hydrophobic materials are “water-avoiding.” One method of defining the hydrophobicity of a polymer is by the solubility parameter of the polymer, also known as the polymer’s cohesive energy density. The solubility parameter is represented by Equation 1:

$$\delta = (\Delta E/V)^{1/2} \quad (\text{Equation 1})$$

where δ = solubility parameter $((\text{cal}/\text{cm}^3)^{1/2})$
 ΔE = energy of vaporization (cal)
 V = molar volume (cm^3)

("Polymer Handbook", 2nd Ed., Brandrup J. and EH Immergut, ed., Wiley-Interscience, John Wiley & Sons, N.Y. (1975)). Because polymers are typically non-volatile and thus cannot be vaporized without decomposition, the solubility parameter is measured indirectly. Briefly, solvents in which a polymer dissolves without a change in heat or volume are identified. The solubility parameter of the polymer is then defined to be the same as the solubility parameters of the identified solvents.

[0020] As a general rule, the value of the solubility parameter δ is inversely proportional to the degree of hydrophobicity of a polymer. Polymers that are very hydrophobic may have a low solubility parameter value. This general proposition is particularly applicable for polymers having a glass transition temperature below physiological temperature. A polymer that is sufficiently hydrophobic for use in the rate-limiting membrane of the present invention can have a solubility parameter of not more than about $10.7 \text{ (cal/cm}^3\text{)}^{1/2}$. Representative examples of such crystalline, hydrophobic polymers include polytetrafluoroethylene, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrenic block copolymers including KRATONTM polymers (available from KRATONTM Polymers, Houston, Texas), ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, poly (vinylidene fluoride), ethylene methacrylic acid copolymers,

polyurethanes with a polydimethylsiloxane soft segment, poly(vinylidene fluoride-co-hexafluoropropene), and polycarbonate urethanes (e.g., BIONATE 55D and BIONATE 75D).

[0021] Polymers of relatively high crystallinity can also maintain their crystallinity in an aqueous environment. Highly crystalline polymers are typically rigid, have high melting temperatures, and are minimally affected by solvent penetration. Since the degree and strength of crystallinity of a polymer can be roughly approximated by the melting temperature of the polymer, sufficiently high crystallinity for use with the present invention is possessed by polymers having a melting temperature greater than or equal to about 135°C at ambient pressure. Representative examples of polymers having a melting temperature of at least 135°C at ambient pressure include, but are not limited to, nylon 6, poly (vinylidene fluoride), poly (vinylidene fluoride-co-hexafluoropropene), polytetrafluoroethylene, polyetheretherketone (PEEK), polyimide, polysulfone, ethylene-co-methacrylic acid, ethylene-co-acrylic acid, and styrenic block copolymers including KRATONTM polymers (available from KRATONTM Polymers, Houston, Texas).

[0022] The above-described suitably crystalline polymers can be used to form a rate-reducing coating onto a medical device. The embodiments of the composition for such a coating can be prepared by conventional methods wherein a predetermined amount of a suitable polymeric compound is added to a predetermined amount of a compatible solvent. "Solvent" is defined as a liquid substance or composition that is mutually compatible with a polymer and is

capable of significantly dissolving the polymer at the concentration desired in the composition. Examples of solvents include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, xylene, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, isopropanol admixed with water, N-methyl pyrrolidinone, toluene, hexafluoroisopropanol, methylene chloride, hexamethylphosphorous triamide, N-methylmorpholine, trifluoroethanol, formic acid, and phenol. The polymeric compound can be added to the solvent at ambient pressure and under anhydrous atmosphere. The polymeric compound is soluble before crystallization in a solvent system at, for example, temperatures of less than or equal to about 80°C. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60°C.

[0023] Application of the composition can be by any conventional method, such as by spraying the composition onto the device or by immersing the device in the composition. Operations such as wiping, centrifugation, blowing, or other web-clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess composition from the surface of the stent; centrifugation refers to rapid rotation of the stent about an axis of rotation; and blowing refers to application of air at a selected pressure to the deposited composition. Any excess composition can also be vacuumed off of the surface of the device. The solvent is removed from the composition to form the rate-reducing

coating by allowing the solvent to evaporate. The evaporation can be induced by heating the device at a predetermined temperature for a predetermined period of time. For example, the device can be heated at a temperature of about 60° C for about 1 hour to about 12 hours. The heating can be conducted in an anhydrous atmosphere and at ambient pressure and should not exceed the temperature that would adversely affect the active agent. The heating can, alternatively, be conducted under a vacuum condition. It is understood that essentially all of the solvent will be removed from the composition, but traces or residues may remain blended with the polymer.

Examples of the Device

[0024] A medical device for use in conjunction with the above-described rate-reducing coating is broadly defined to include any inter- or intraluminal device used for the release of an active agent and/or for upholding the luminal patency in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, anastomosis devices such as axius coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of

cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

Use of the Rate-Reducing Coating

[0025] In one embodiment, the above-described rate-reducing coating, free from therapeutic substances or active agents, can function as a barrier layer through which an underlying therapeutic substance or active agent must diffuse to be released from a device into a treatment site. The active agent can be carried by the device, such as in porous cavities in the surface of the device, or can be impregnated in a reservoir polymer layer formed beneath the rate-reducing coating. Such a rate-reducing barrier coating can be of any suitable thickness. The thickness of the coating can be from about 0.01 microns to about 20 microns, more narrowly from about 0.1 microns to about 10 microns. By way of example, the rate-reducing barrier coating can have a thickness of about 3 microns.

[0026] In another embodiment, the rate-reducing coating can additionally function as a reservoir for carrying the therapeutic substance or active agent. In such an embodiment, sufficient amounts of an active agent can be dispersed in the blended composition of the suitably crystalline polymer and the solvent. The polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can

comprise from about 59.9% to about 99.8%, more narrowly from about 79% to about 89% by weight of the total weight of the composition, and the active agent can comprise from about 0.1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition.

[0027] The active agent should be in true solution or saturated in the blended composition. If the active agent is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The active agent may be added so that the dispersion is in fine particles.

[0028] The active agent can be for inhibiting the activity of vascular smooth muscle cells. More specifically, the active agent can be aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells for the inhibition of restenosis. The active agent can also include any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. For example, the agent can be for enhancing wound healing in a vascular site or improving the structural and elastic properties of the vascular site. Examples of agents include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. The active agent can also fall under the genus of antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances.

Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL[®] by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere[®], from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin[®] from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin[®] from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax[™] (Biogen, Inc., Cambridge, Mass.).

Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten[®] and Capozide[®] from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil[®] and Prinzide[®] from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor[®] from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an

antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, rapamycin and dexamethasone. Exposure of the active agent to the composition should not adversely alter the active agent's composition or characteristic. Accordingly, the particular active agent is selected for compatibility with the solvent or blended polymer-solvent.

[0029] In one embodiment, an optional primer layer can be formed on the outer surface of the medical device. Formation of a primer layer, free from any active agents, can be by any conventional method, such as by spraying a primer composition containing a polymer and a compatible solvent onto the medical device or immersing the medical device in the primer composition followed by evaporation of the solvent. The polymer selected can be any polymer suitable for coating a medical device. With the use of thermoplastic polymers such as, but not limited to, ethylene vinyl alcohol copolymer, polycaprolactone, poly(lactide-co-glycolide), and poly(hydroxybutyrate), the deposited primer composition should be exposed to a heat treatment at a temperature range greater than about the glass transition temperature (T_g) and less than about the melting temperature (T_m) of the selected polymer. Unexpected results have been discovered with treatment of the composition under this temperature range, specifically strong adhesion or bonding of the coating to the metallic surface of a stent. The medical device should be exposed to the heat treatment for any suitable duration of time that will allow for the formation of the primer layer on the outer surface of the device and for the evaporation of the solvent employed. It is understood that essentially all of the

solvent will be removed from the primer composition but traces or residues can remain blended with the polymer.

[0030] In other embodiments, the crystalline coating can be topcoated with one or more additional coating layers. Such additional coating layers can be for increasing the biocompatibility of the device. For example, in one embodiment, the additional coating layer can be formed from ethylene vinyl alcohol (EVAL), polyethylene glycol, polyethylene oxide, hyaluronic acid, heparin, or heparin derivatives having hydrophobic counterions, thereby providing biocompatibility to the outermost, tissue-contacting surface of the medical device.

[0031] In another embodiment, an additional coating layer can serve as yet another rate-reducing layer. Because the additional rate-reducing layer does not contain active agents, the methods by which such a layer is deposited is not limited to the methods by which the polymer layers having active agents are applied. Therefore, in addition to application by conventional methods, such as by spraying a polymeric composition onto the device or by immersing the device in a polymeric composition, the additional rate-reducing layers can be deposited by physical vapor deposition (PVD) techniques, which are known to one of ordinary skill in the art. Representative examples of barrier materials that can be deposited via PVD techniques include plasma-deposited polymers, parylene C, parylene N, parylene D, perfluoro parylene, tetrafluoro (AF4) parylene, metallic layers, metallic oxides, metal carbides, and metal nitrides.

Methods of Use

[0032] In accordance with embodiments of the above-described method, an active agent can be applied to an implantable medical device or prosthesis, e.g., a stent, retained on the stent during delivery and expansion of the stent, and released at a desired control rate and for a predetermined duration of time at the site of implantation. A stent having the above-described coating is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating is particularly useful for treating occluded regions of blood vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries.

[0033] Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. An angiogram is typically accomplished by injecting a radiopaque contrasting agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter that allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above-described coating may then be

expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

[0034] The embodiments of the invention will be illustrated by the following set forth prophetic examples, which are being given by way of illustration only and not by way of limitation. All parameters are not to be construed to unduly limit the scope of the embodiments of the invention.

Example 1

[0035] A 2% (w/w) solution of EVAL in dimethylacetamide (DMAC) is applied to a 13 mm TetraTM stent (available from Guidant Corporation) using an EFD 780S spray device (available from EFD Inc., East Providence, RI) until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 140°C for 60 minutes to form a primer layer on the stent. A solution of 1:9 (w/w) actinomycin D:EVAL and 2% (w/w) EVAL in DMAC is sprayed onto the primed stent until 100 micrograms of solids have been deposited. The stent is baked at 50°C for 2 hours to form an actinomycin D-containing reservoir coating. A 2% (w/w) polyvinylidene fluoride solution in DMAC is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 50°C for 2 hours to form a crystalline rate-reducing membrane of polyvinylidene fluoride.

Example 2

[0036] A 2% (w/w) solution of EVAL in DMAC is applied to a 13 mm Tetra™ stent using an EFD 780S spray device until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 140°C for 60 minutes to form a primer layer on the stent. A solution of 1:3 (w/w) dexamethasone:poly(ethylene-co-vinyl-acetate) and 2% (w/w) poly(ethylene-co-vinyl-acetate) in cyclohexanone is sprayed onto the primed stent until 300 micrograms of solids have been deposited. The stent is baked at 60°C for 2 hours to form a dexamethasone-containing reservoir coating. A 2% (w/w) KRATON G1650 (available from KRATON™ Polymers, Houston, Texas) solution in xylene is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 60°C for 2 hours to form a crystalline rate-reducing membrane of KRATON G1650.

Example 3

[0037] A 2% (w/w) solution of EVAL in DMAC is applied to a 13 mm Tetra™ stent using an EFD 780S spray device until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 140°C for 60 minutes to form a primer layer on the stent. A solution of 1:2 (w/w) estradiol:EVAL and 2% (w/w) EVAL in DMAC is sprayed onto the primed stent until 350 micrograms of solids have been deposited. The stent is baked at 60°C for 2 hours to form an estradiol-containing reservoir coating. A 2% (w/w) poly(vinylidene fluoride-co-hexafluoropropene) solution in 1:1 (w/w) acetone:DMAC is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 60°C for 2 hours to form a crystalline rate-reducing membrane of poly(vinylidene fluoride-co-hexafluoropropene).

Example 4

[0038] A 2% (w/w) solution of poly(n-butyl methacrylate) in 4:1 (w/w) acetone:cyclohexanone is applied to a 13 mm TetraTM stent using an EFD 780S spray device until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 70°C for 60 minutes to form a primer layer on the stent. A solution of 1:2 (w/w) etoposide:EVAL and 2% (w/w) EVAL in DMAC is sprayed onto the primed stent until 300 micrograms of solids have been deposited. The stent is baked at 60°C for 2 hours to form an etoposide-containing reservoir coating. A 1.5% (w/w) silicone-urethane Elast-EonTM 55D (available from Elastomedic Pty Ltd., Australia) solution in 1:1 (w/w) THF:DMAC is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 60°C for 2 hours to form a crystalline rate-reducing membrane of silicone-urethane Elast-EonTM 55D.

[0039] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

What is claimed is:

1. A stent for delivery of a therapeutic agent, comprising:
a polymer coating for reducing the rate of release of the therapeutic agent, the polymer having a crystalline structure, wherein the polymer is capable of significantly maintaining the crystalline structure while the therapeutic agent is released from the stent such that the aqueous environment to which the stent is exposed subsequent to the implantation of the stent does not significantly convert the crystalline structure of the polymer to an amorphous structure.
2. The stent of Claim 1, wherein the crystallinity of the polymer is not less than about 50% prior to the implantation of the stent or not less than about 25% when exposed to the aqueous environment subsequent to the implantation of the stent.
3. The stent of Claim 1, wherein the melting point of the polymer is greater than or equal to about 135°C at ambient pressure.
4. The stent of Claim 1, wherein the polymer is a hydrophobic polymer having a solubility parameter of not more than about $10.7 \text{ (cal/cm}^3)^{1/2}$.
5. The stent of Claim 1, wherein the polymer is selected from a group of polytetrafluoroethylene, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropene, low density linear

polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, styrenic block copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, poly(vinylidene fluoride-co-hexafluoropropene), poly(vinylidene fluoride), and polycarbonate urethanes.

6. The stent of Claim 1, wherein the polymer is selected from a group of nylon 6, polytetrafluoroethylene, polyetheretherketone, polyimide, polysulfone, ethylene-co-methacrylic acid, ethylene-co-acrylic acid, poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene) and styrenic block copolymers.

7. The stent of Claim 1, wherein the coating contains the therapeutic agent for delivery of the therapeutic agent.

8. The stent of Claim 7, additionally comprising:

a primer layer formed on the surface of the medical device, wherein the coating is formed over the primer layer, and wherein the primer layer acts as an adhesive tie between the coating and the surface of the medical device.

9. The stent of Claim 1, additionally comprising:
a reservoir layer containing the therapeutic agent formed on the medical device, wherein the coating is formed over at least a region of the reservoir layer to reduce the rate of release of the therapeutic agent.
10. The stent of Claim 1, additionally comprising:
a primer layer formed on the surface of the medical device; and
a reservoir layer containing the therapeutic agent formed on the primer layer, wherein the coating is formed on at least a portion of the reservoir layer to reduce the rate of release of the therapeutic agent.
11. A method of forming a coating for a stent for reducing the rate of release of a therapeutic agent from the stent, comprising:
applying a first composition including a polymeric material to at least a portion of the stent to form a polymer coating supported by the stent, the polymer having a crystalline structure, wherein the aqueous environment to which the coating is exposed subsequent to the implantation of the stent does not significantly convert the crystalline structure of the polymer to an amorphous structure for the duration of time which the agent is released from the stent.
12. A stent comprising a polymeric coating, the coating being produced in accordance with the method of Claim 11.

13. The method of Claim 11, wherein the crystallinity of the polymeric material is not less than about 25% during the release of the therapeutic agent from the stent.

14. The method of Claim 11, wherein the polymeric material has a solubility parameter not more than about $10.7 \text{ (cal/cm}^3\text{)}^{1/2}$.

15. The method of Claim 11, wherein the polymeric material has a melting point greater than or equal to about 135°C at ambient pressure.

16. The method of Claim 11, wherein the polymer is selected from a group of polytetrafluoroethylene, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropene, poly(vinylidene fluoride), low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrenic block copolymers, ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, poly(vinylidene fluoride-co-hexafluoropropene), and polycarbonate urethanes.

17. The method of Claim 11, wherein the polymer is selected from a group of nylon 6, polytetrafluoroethylene, polyetheretherketone, polyimide, polysulfone, ethylene-co-methacrylic acid, ethylene-co-acrylic acid,

poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene), and styrenic block copolymers.

18. A composition for coating a stent, comprising:

a) a fluid; and

b) a polymer dissolved in the fluid, wherein the polymer comprises a crystalline structure during the duration of delivery of an active agent from the stent and wherein the aqueous environment to which the stent is exposed subsequent to the implantation procedure does not significantly change the crystalline structure to an amorphous structure.

19. A stent for delivering a therapeutic agent to an implanted site, comprising:

a radially expandable body structure; and

a polymeric coating supported by the body structure for extending the residence time of the therapeutic agent at the implanted site, wherein the polymeric coating is made from a hydrophobic polymer having a degree of crystallinity that remains at or above about 10% at least until a significant amount of the therapeutic substance has been released from the stent.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/27521

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L31/10 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 023 879 A (MEDTRONIC INC) 2 August 2000 (2000-08-02) claims; examples	1-19
X	US 5 980 972 A (DING NI) 9 November 1999 (1999-11-09) column 3, line 17 - line 51; claims	1-19
X	WO 01 45763 A (ADVANCED CARDIOVASCULAR SYSTEM) 28 June 2001 (2001-06-28) claims; examples	1-19
X	US 4 977 901 A (OFSTEAD RONALD F) 18 December 1990 (1990-12-18) claims; examples	1-19
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 November 2002

Date of mailing of the international search report

25/11/2002

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

ESPINOSA, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/27521

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 850 651 A (SCHNEIDER USA INC) 1 July 1998 (1998-07-01) claims; examples	1,5
X	EP 0 627 226 A (IST NAZ STUD CURA DEI TUMORI) 7 December 1994 (1994-12-07) claims; examples	1,5
A	EP 0 970 711 A (ETHICON INC) 12 January 2000 (2000-01-12) claims; examples	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/27521

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1023879	A	02-08-2000	EP 1023879 A2	02-08-2000
US 5980972	A	09-11-1999	CA 2225096 A1	20-06-1998
			EP 0850651 A2	01-07-1998
			JP 10192413 A	28-07-1998
WO 0145763	A	28-06-2001	AU 2449601 A	03-07-2001
			EP 1242130 A1	25-09-2002
			WO 0145763 A1	28-06-2001
			US 2001014717 A1	16-08-2001
			US 2001018469 A1	30-08-2001
US 4977901	A	18-12-1990	AU 643669 B2	25-11-1993
			AU 4445889 A	31-05-1990
			CA 2001888 A1	23-05-1990
			EP 0370657 A2	30-05-1990
			JP 2200271 A	08-08-1990
EP 0850651	A	01-07-1998	CA 2225096 A1	20-06-1998
			EP 0850651 A2	01-07-1998
			JP 10192413 A	28-07-1998
			US 5980972 A	09-11-1999
EP 0627226	A	07-12-1994	IT MI931176 A1	05-12-1994
			AT 174517 T	15-01-1999
			DE 69415212 D1	28-01-1999
			DE 69415212 T2	12-05-1999
			DK 627226 T3	23-08-1999
			EP 0627226 A1	07-12-1994
			ES 2124811 T3	16-02-1999
			US 5779729 A	14-07-1998
EP 0970711	A	12-01-2000	US 6153252 A	28-11-2000
			EP 0970711 A2	12-01-2000
			JP 2000051367 A	22-02-2000

